

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 08-259465

(43)Date of publication of application : 08.10.1996

(51)Int.Cl.

A61K 45/00
A61K 31/19
A61K 31/35
A61K 31/405
A61K 31/54
A61K 47/10
//(A61K 31/19
A61K 31:35)
(A61K 31/405
A61K 31:35)
(A61K 31/54
A61K 31:35)

(21)Application number : 07-067491

(71)Applicant : SEKISUI CHEM CO LTD

(22)Date of filing : 27.03.1995

(72)Inventor : SHIMIZU TATSUTAKE
HORIGUCHI TOMOKO
KURIYAMA KIYOSHI

(54) EXTERNAL PREPARATION FOR TREATING SKIN DISEASE

(57)Abstract:

PURPOSE: To obtain an external preparation containing a nonsteroidal anti-inflammatory agent and sodium cromoglycate as active ingredients, hardly having adverse effects, having pharmacodynamic effects at least comparable to adrenocortical hormones and useful for treating skin diseases.

CONSTITUTION: This external preparation contains preferably 1 to 60wt.% of a non-steroidal anti-inflammatory agent such as indomethacin, piroxicam, ketoprofen, flurbiprofen or felbinac, preferably 1 to 60wt.% of sodium cromoglycate, preferably 1 to 60wt.% of propylene glycol and if necessary, percutaneous absorption absorbefacient.

LEGAL STATUS

[Date of request for examination]

12.11.2001

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than withdrawal
the examiner's decision of rejection or
application converted registration]

[Date of final disposal for application] 02.04.2004

[Patent number]

[Date of registration]

[Number of appeal against examiner's
decision of rejection]

[Date of requesting appeal against examiner's
decision of rejection]

[Date of extinction of right]

Copyright (C); 1998,2003 Japan Patent Office

* NOTICES *

JPO and NCIPi are not responsible for any damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

CLAIMS

[Claim(s)]

[Claim 1] A non steroid anti-inflammatory agent, disodium cromoglycate, and external preparations for a skin disease therapy characterized by containing propylene glycol.

[Claim 2] External preparations for a skin disease therapy according to claim 1 characterized by a non steroid anti-inflammatory agent being more than a kind chosen from the group which consists of indomethacin, piroxicam, ketoprofen, flurbiprofen, or felbinac.

[Claim 3] External preparations for a skin disease therapy according to claim 1 or 2 with which the content of a non steroid anti-inflammatory agent is characterized by the content of disodium cromoglycate being [the content of 1 - 60 % of the weight and propylene glycol] 1 - 60 % of the weight one to 60% of the weight.

[Translation done.]

* NOTICES *

JPO and NCIPi are not responsible for any damages caused by the use of this translation.

- 1.This document has been translated by computer. So the translation may not reflect the original precisely.
- 2.**** shows the word which can not be translated.
- 3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the external preparations for a skin disease therapy.

[0002]

[Description of the Prior Art] Conventionally the external preparations which consist of synthetic adenocorticotrophic hormone are widely used for the therapy of intractable skin disease, such as cutaneous sensitization and atopic dermatitis, and it is known that the pharmacology effectiveness is high (month-long drug regulatory affairs; 26, 8, 55, and 1984). Moreover, although the external preparations which consist of a non steroid anti-inflammatory agent or an antihistamine are also used, as compared with adenocorticotrophic hormone external preparations, the effectiveness over the above intractable skin disease is not enough (a new drug and a therapy; 35, 298, 1984).

[0003] However, if the drugs by which a possibility of causing side effects, such as infectible sthenia, thinning of the skin, embrittlement of a blood vessel wall, and abnormality activation of a trichocyst sebaceous gland system, is upwards to the application site, and percutaneous absorption was carried out may cause a generalized side effect and reduce a dose conversely, in order that effectiveness may decrease, an administration period is extended, and synthetic adenocorticotrophic hormone external preparations have a possibility that a side effect may get worse further.

[0004] On the other hand, safety of disodium cromoglycate is high, for example, it is widely used to an allergic disease or chronic dermatitis as indicated by the Patent Publication Heisei No. 501714 [five to] official report, and JP,3-118321,A. Moreover, indomethacin, piroxicam, ketoprofen, flurbiprofen, or felbinac is a non steroid anti-inflammatory agent, and is used to symptoms, such as the osteoarthritis, a frozen shoulder, tenovaginitis, peritendinitis, humerus epicondylitis, muscular pain, and swelling, a pain after a trauma, as external preparations.

[0005] However, disodium cromoglycate was used together with non steroid anti-inflammatory agents, such as indomethacin, piroxicam, ketoprofen, flurbiprofen, and felbinac, and it was not indicated about using for skin disease as external preparations until now.

[0006]

[Problem(s) to be Solved by the Invention] The place which this invention solves the above-mentioned trouble and is made into the purpose has few side effects, and it is offering adenocorticotrophic hormone external preparations and the external preparations for a skin disease therapy which have the drug effect more than an EQC moreover.

[0007]

[Means for Solving the Problem] The external preparations for a skin disease therapy of this invention contain a non steroid anti-inflammatory agent, disodium cromoglycate (referred to as "DSCG" cromolyn and below DISODIUMUKUROMOGURIKETO;), and propylene glycol.

[0008] As the above-mentioned non steroid anti-inflammatory agent, for example Indomethacin, piroxicam, Ketoprofen, flurbiprofen, felbinac, tenoxicam, Oxaprozin, tiaprofenic acid, fentiazac, bucolome, Tolmetin sodium, acemetacine, emorfazone, tiaramide hydrochloride, Mepirizole, tinoridine

hydrochloride, loxoprofen sodium, pranoprofen, Fenoprofen calcium, naproxen, ibuprofen, aluminoprofen, Diflunisal, floctafenine, flufenamic acid, flufenamic acid aluminium, It is desirable to contain more than a kind chosen from the group which mefenamic acid, tolfenamic acid, etc. are especially mentioned, among these consists of indomethacin, piroxicam, ketoprofen, flurbiprofen, or felbinac.

[0009] Adoption of the above-mentioned indomethacin and the ketoprofen is carried out to the Japanese pharmacopoeia as an antiinflammatory drug, and an antiallergic drug is used as an antiinflammatory drug and, as for them, piroxicam, flurbiprofen, and felbinac are also widely used as an antiasthmatic drug, as for DSCG.

[0010] Although the content in a non steroid anti-inflammatory agent and the external preparations of DSCG changes with classes of non steroid anti-inflammatory agent, since effectiveness becomes less enough when will not dissolve in a basis if it increases, but it becomes impossible to hold a pharmaceutical form especially in the case of ointment or a cream and it decreases, its 1 - 60 % of the weight is desirable, and it is 10 - 30 % of the weight still more preferably five to 40% of the weight more preferably.

[0011] Although the above-mentioned propylene glycols are a non steroid anti-inflammatory agent and the solvent of DSCG and the content in external preparations changes with a non steroid anti-inflammatory agent and amounts of DSCG, since a non steroid anti-inflammatory agent and DSCG will not dissolve if it becomes impossible to hold a pharmaceutical form and decreases when it increased and considers as pharmaceutical preparation, 1 - 60 % of the weight is desirable.

[0012] In this invention, penetration enhancer contains in external preparations if needed. Since the percutaneous absorption effectiveness of a drug becomes less enough when there is a possibility of especially the curative effect of DSCG and a non steroid anti-inflammatory agent not increasing, but causing a skin stimulus etc. conversely if the content in the external preparations of the above-mentioned absorption enhancers increases and it decreases, 0.3 - 30 % of the weight is 0.5 - 10 % of the weight desirable still more preferably.

[0013] As the above-mentioned penetration enhancer, fatty acid ester, the compound which has amide association, the divalent carboxylic acid of carbon numbers 2-10 and its salt, polyoxyethylene-alkyl-ether phosphoric ester and its salt, a lactic acid, lactate, a citric acid, etc. are mentioned, for example.

[0014] The above-mentioned fatty acid ester is the resultant of the fatty acid of carbon numbers 10-18, and the alcohol of carbon numbers 1-20. As a fatty acid of the above-mentioned carbon numbers 10-18, unsaturated fatty acid, such as saturated fatty acid; oleic acid, such as a capric acid, undecylic acid, a lauric acid, a tridecyl acid, a myristic acid, a palmitic acid, and stearin acid, linolic acid, and a linolenic acid, etc. is mentioned, for example.

[0015] As alcohol of the above-mentioned carbon numbers 1-20, aliphatic series unsaturated alcohol, such as aliphatic series saturated alcohol, such as a methanol, ethanol, propanol, isopropanol, a butanol, isobutanol, amyl alcohol, isoamyl alcohol, a hexanol, heptanol, an octanol, capryl lactam alcohol, nonyl alcohol, decyl alcohol, lauryl alcohol, myristyl alcohol, palmityl alcohol, and stearyl alcohol, and allyl alcohol, etc. is mentioned, for example. As the above-mentioned fatty acid ester, myristic-acid isopropyl, palmitic-acid isopropyl, lauric-acid isopropyl, stearin acid isopropyl, etc. are mentioned, for example.

[0016] As a compound which has the above-mentioned amide association, N-acyl sarcosine, fatty-acid monochrome or diethanolamide, these alkylene oxide addition products, etc. are mentioned, for example. As the above-mentioned N-acyl sarcosine, an N-lauroyl sarcosine etc. is mentioned, for example. As the above-mentioned fatty-acid monochrome or diethanolamide, and these alkylene oxide addition products, lauroyl monoethanol amide, palmitic-acid monoethanolamide, myristic-acid diethanolamide, a lauric acid and myristic-acid diethanolamide, palm-oil-fatty-acid monoethanolamide, polyoxyethylene addition lauroyl monoethanol amide, polyoxyethylene addition palm-oil-fatty-acid monoethanolamide, etc. are mentioned, for example.

[0017] As the divalent carboxylic acid of the above-mentioned carbon numbers 2-10, and its salt, salts, such as these sodium salt, such as oxalic acid, a malonic acid, a fumaric acid, a maleic acid, a tartaric

acid, a malic acid, a succinic acid, a glutaric acid, an adipic acid, a fumaric acid, isophthalic acid, and a terephthalic acid, and potassium salt, magnesium salt, and an aluminum salt, are mentioned, for example.

[0018] The above-mentioned polyoxyethylene-alkyl-ether phosphoric ester and its salt They are the phosphoric ester of the derivative obtained by carrying out the addition polymerization of the ethylene oxide to alcohol, and its salt. As an alkyl group For example, a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, t-butyl, a pentyl radical, a hexyl group, a heptyl radical, an octyl radical, A nonyl radical, a decyl group, the dodecyl, a lauryl radical, a stearyl radical, a palmityl radical, the Millis Chill radical, a cetyl group, etc. are mentioned, and sodium salt, potassium salt, magnesium salt, an aluminum salt, etc. are mentioned as a salt, for example. As the above-mentioned lactate, the ester of a lactic acid and the alcohol of carbon numbers 1-20 is mentioned, for example, lactic-acid Millis Chill, lactic-acid cetyl, etc. are mentioned. Especially as penetration enhancer, fatty acid ester and N-acyl sarcosine are desirable among the above.

[0019] Especially the pharmaceutical form of the external preparations of this invention is not limited, and the gestalt of a cream, a paste, gel, ointment, a milky lotion, a lotion, the liniment, a mousse, a spray, or a solution, patches, etc. are mentioned. When fabricating in the gestalt of a cream, a paste, gel, ointment, a milky lotion, a lotion, the liniment, or a solution, a well-known thing can be conventionally used as a basis if needed, for example, ointment bases, such as vaseline, yellow bees wax, and hydro carbon gel ointment (for example, trade name Plastibase, Taisho Pharmaceutical Co., Ltd. make), a liquid paraffin, a polyethylene glycol, a cellulose, alcohol, water, starch, olive oil, etc. are mentioned.

[0020] The external preparations of this invention are manufactured by the usual approach of often kneading a basis each component and if needed, and it applies to the affected part directly, or they are used by the anticipated-use approach of infiltrating cloth etc. and applying.

[0021] Although the dosage of the external preparations for a skin disease therapy of this invention changes with the class of non steroid anti-inflammatory agent to blend and the class of disease, extent of a symptom, magnitude of the affected part, etc., as an amount of DSCG and a non steroid anti-inflammatory agent, they are 0.02-1g preferably per day, and divides and applies this to a suitable count.

[0022] As skin disease set as the therapy object of the external preparations of this invention Skin disease including the adaptation disease of the conventional synthetic adrenocorticotrophic hormone external preparations is mentioned. For example, atopic dermatitis, cutaneous sensitization, the seborrheic dermatitis, a VIDARU lichen, The eczema nummulare, housewives eczema, solar dermatitis, *****, the skin itch, the itch, a drug rash, The toxicoderma, psoriasis, the parapsoriasis, palmoplantar pustulosis, a flat lichen, the lichen nitidus, pityriasis rubra pilaris, Gilbert's rose pityriasis, an erythema group, the erythroderma, discoid lupus erythematosus, systemic lupus erythematosus, pemphigus, pemphigoid, Duhring dermatitis herpetiformis, alopecia areata, simple nature facula, sarcoidosis, the amyloidosis cutis, keloid, a hypertrophic scar, etc. are mentioned.

[0023] The pharmacological action of the external preparations for an intractable skin disease therapy of this invention Like the below-mentioned example, as a laboratory animal model of the nonallergic skin inflammatory response of a rat, and I-beam allergy A rat 4-hour passive-cutaneous-anaphylaxis (homologous PCA) reaction of the same kind, And the rat delayed type skin allergic reaction (DTH) was shown as a laboratory animal model of IV mold allergy, and the effectiveness more than an EQC was acquired for the skin external preparations containing DSCG and the non steroid anti-inflammatory agent of the amount of business as compared with the external preparations of only adrenocorticotrophic hormone.

[0024]

[Example] This invention is explained per example.

(An example and example of a comparison) For each component, such as DSCG of the presentation shown in Tables 1-5, a non steroid anti-inflammatory agent, propylene glycol, and absorption enhancers, the ointment could add Plastibase (Taisho Pharmaceutical Co., Ltd. make), liniments could add olive oil as a basis, it kneaded, and the external preparations for a skin disease therapy of each example and the

example of a comparison were obtained for it so that the whole quantity might be further set to 100.

[0025] In addition, the following were used as things other than a basis.

- Disodium cromoglycate (DSCG, sigma company make)
- Indomethacin (sigma company make)
- N-lauroyl sarcosine (Nakarai Tesuku make)
- Piroxicam (sigma company make)
- Ketoprofen (sigma company make)
- Flurbiprofen (sigma company make)
- Felbinac (sigma company make)

[0026] "Disodium cromoglycate" and "IM" "DS" of front Naka Moreover, "indomethacin", "PC" "ketoprofen" and "FP" for "piroxicam" and "KP" "Flurbiprofen", In "myristic-acid isopropyl" and "LS", an "N-lauroyl sarcosine" and "DM" express "dexamethasone" and "PD" expresses ["FN" is "felbinac" and "PG" / "propylene glycol" and "IP"] "prednisolone", respectively.

[0027]

[Table 1]

	剤 型	組 成 (重量%)							試 験 例			
		DS	IM	PG	吸収促進剤 IP	LS	副腎皮質ホルモン DM	PD	1 (%)	2 (%)	3 (%)	4 (g)
実施例 1	軟 膏	2	2	8	1	—	—	—	40.6	39.6	40.3	168
実施例 2	リゾット	2	2	8	1	—	—	—	39.8	39.2	39.6	167
実施例 3	軟 膏	10	10	40	1	—	—	—	43.0	42.9	43.3	169
実施例 4	リゾット	10	10	40	1	—	—	—	41.2	40.1	41.5	167
実施例 5	軟 膏	2	2	8	—	1	—	—	42.3	43.2	40.7	165
実施例 6	リゾット	2	2	8	—	1	—	—	41.9	42.6	40.2	163
実施例 7	軟 膏	15	15	60	—	—	—	—	28.6	27.9	25.8	166
実施例 8	リゾット	15	15	60	—	—	—	—	29.2	28.1	24.6	167
比較例 1	軟 膏	—	—	10	1	—	0.05	—	36.1	41.2	41.6	139
比較例 2	軟 膏	—	—	10	1	—	—	0.5	34.2	38.8	39.2	141
比較例 3	軟 膏	0.5	0.5	2	1	—	—	—	11.0	14.3	12.2	166
比較例 4	軟 膏	10	—	20	1	—	—	—	4.6	24.8	2.5	166
比較例 5	軟 膏	—	10	20	1	—	—	—	3.6	3.8	19.8	167
コントロール	—	—	—	—	—	—	—	—	0	0	0	168

[0028]

[Table 2]

	剤 型	組 成 (重量%)					試 験 例			
		DS	PC	PG	吸収促進剤 IP LS		1 (%)	2 (%)	3 (%)	4 (g)
実施例 9	軟 膏	2	2	8	1	—	39.8	38.6	37.6	169
実施例 10	リゾット	2	2	8	1	—	37.9	36.5	35.4	168
実施例 11	軟 膏	10	10	40	1	—	41.8	40.0	41.3	168
実施例 12	リゾット	10	10	40	1	—	40.1	39.8	40.2	166
実施例 13	軟 膏	2	2	8	—	1	38.8	39.1	39.8	164
実施例 14	リゾット	2	2	8	—	1	38.9	37.5	38.3	165
実施例 15	軟 膏	15	15	60	—	—	27.9	26.2	24.3	167
実施例 16	リゾット	15	15	60	—	—	27.8	24.6	23.2	167
比較例 6	軟 膏	0.5	0.5	2	1	—	10.8	12.1	11.6	169
比較例 7	軟 膏	10	—	20	1	—	4.6	24.8	2.5	167
比較例 8	軟 膏	—	10	20	1	—	3.6	3.8	9.6	165

[0029]

[Table 3]

	剤 型	組 成 (重量%)					試 験 例			
		DS	KP	PG	吸収促進剤 IP LS		1 (%)	2 (%)	3 (%)	4 (g)
実施例 17	軟 膏	2	2	8	1	—	41.1	39.8	42.1	167
実施例 18	リゾット	2	2	8	1	—	40.2	40.1	41.3	164
実施例 19	軟 膏	10	10	40	1	—	42.2	41.8	44.1	168
実施例 20	リゾット	10	10	40	1	—	42.0	39.6	40.5	166
実施例 21	軟 膏	2	2	8	—	1	41.6	41.8	39.5	163
実施例 22	リゾット	2	2	8	—	1	40.1	41.4	39.9	164
実施例 23	軟 膏	15	15	60	—	—	29.7	28.8	26.1	165
実施例 24	リゾット	15	15	60	—	—	30.0	29.5	25.1	168
比較例 9	軟 膏	0.5	0.5	2	1	—	13.4	15.2	11.8	169
比較例 10	軟 膏	10	—	20	1	—	3.7	26.9	2.8	168
比較例 11	軟 膏	—	10	20	1	—	2.8	2.9	9.8	166

[0030]

[Table 4]

	剤 型	組 成 (重量%)					試 験 例			
		DS	FP	PG	吸収促進剤 IP LS		1 (%)	2 (%)	3 (%)	4 (g)
実施例 25	軟 膏	2	2	8	1	—	41.3	40.2	41.8	168
実施例 26	リゾット	2	2	8	1	—	39.8	41.1	40.8	166
実施例 27	軟 膏	10	10	40	1	—	41.9	40.6	44.3	169
実施例 28	リゾット	10	10	40	1	—	41.8	40.1	39.9	167
実施例 29	軟 膏	2	2	8	—	1	42.1	41.2	39.8	164
実施例 30	リゾット	2	2	8	—	1	39.9	40.8	40.1	165
実施例 31	軟 膏	15	15	60	—	—	30.1	29.0	27.1	164
実施例 32	リゾット	15	15	60	—	—	31.1	30.0	24.8	167
比較例 12	軟 膏	0.5	0.5	2	1	—	12.8	16.1	10.9	168
比較例 13	軟 膏	10	—	20	1	—	3.7	26.9	2.8	168
比較例 14	軟 膏	—	10	20	1	—	2.6	3.0	10.1	165

[0031]

[Table 5]

	剤 型	組 成 (重量%)					試 験 例			
		DS	FN	PG	吸収促進剤 IP LS		1 (%)	2 (%)	3 (%)	4 (g)
実施例 33	軟 膏	2	2	8	1	—	42.6	38.9	41.6	166
実施例 34	リゾット	2	2	8	1	—	40.0	39.9	42.1	163
実施例 35	軟 膏	10	10	40	1	—	41.8	42.3	42.5	167
実施例 36	リゾット	10	10	40	1	—	41.8	40.6	39.2	165
実施例 37	軟 膏	2	2	8	—	1	40.5	42.6	41.0	164
実施例 38	リゾット	2	2	8	—	1	41.6	42.1	38.8	166
実施例 39	軟 膏	15	15	60	—	—	28.8	29.0	25.4	167
実施例 40	リゾット	15	15	60	—	—	31.2	28.7	24.6	165
比較例 15	軟 膏	0.5	0.5	2	1	—	13.6	16.2	12.9	170
比較例 16	軟 膏	10	—	20	1	—	3.7	26.9	2.8	166
比較例 17	軟 膏	—	10	20	1	—	2.4	3.0	10.1	168

[0032] [Example 1 of a trial] Carried out trimming of the antinode flank skin of the seven week ** Wistar system rat of the operation effectiveness to the nonallergic skin inflammatory response by the DNCB induction skin primary stimulative reaction, and subsequently did 20microl spreading of a 2,4-dinitrochlorobenzene (DNCB, Wako Pure Chem make) acetone solution 2%, it was made to often dry, and nonallergic dermatitis was induced. subsequently, the 0.1ml sample offering agent of the 0.1mg or liniments of the ointment obtained in the above-mentioned example and the example of a comparison -- applying each so that an ointment might put on a rat skin DNCB reaction induction part at the piece of a circular polyethylene sheet with a radius of 1cm and the skin might be touched, liniments were dropped at the direct skin, and covered and applied a it top by the piece of a circular polyethylene sheet with a radius of 1cm.

[0033] 24 hours after reaction induction, the erythema reinforcement of a reactive site was measured with the color difference meter (CR-200, Minolta Co., Ltd. make). As control, only an ointment base or olive oil was similarly applied instead of the above-mentioned sample offering agent, same actuation was performed after that, and erythema reinforcement was measured. From the measurement result of the erythema reinforcement (A) of the above-mentioned control application site, and the erythema reinforcement (B) of a sample offering agent application site, the rate of erythema control was computed by the following formula. A result is shown in Tables 1-5.

Rate (%) of erythema control = $\{(A-B) / A\} \times 100$ [0034] [Example 2 of a trial] Preparation of an operation effectiveness (1) rat anti-DNP-As blood serum to the I-beam allergic response by PCA reaction and According to the approach (1002 Journal of Immunology;106 and 1971) of Okumura, the rat anti-DNP-As blood serum was prepared. It is Strejan about the extract of *Ascaris suum* (*Ascarisuum*). and It extracted according to the approach (893 Journal of Immunology;98 and 1967) of Campbell, subsequently this was combined with 2,4-dinitrophenyl sulfate (DNP) by Eisen's and others approach (4583 Journal of American Chemical Society;75 and 1953), and the DNP association *Ascarisuum* (DNP-As) was obtained.

[0035] 1mg of above-mentioned DNP-As was dissolved in 1ml of physiological sodium chloride solution which made 1×10^{10} pertussis killed bacteria float, and hypodermically [of the feminity rat before and behind the weight of 200g / limbs planta] was injected. 0.5mg of DNP-As was dissolved in 0.5ml of physiological sodium chloride solution five days after, and intramuscular on either side was injected. It collected blood from the abdominal aorta eight days after first time injection, the blood serum was separated, and the rat anti-DNP-As blood serum was obtained.

[0036] (2) The PCA reaction above-mentioned rat anti-DNP-As blood serum was diluted with physiological sodium chloride solution, and it injected with the 0.05ml in the regions-of-back hide of a with a weights [120-200g] male rat. the 0.1ml sample offering agent of the 0.1mg and liniments of the ointment obtained in the above-mentioned example and the example of a comparison 45 hours after -- each was applied to the anti-DNP-As blood serum injection site of the rat skin by the same approach as the above-mentioned example 1 of a trial. Furthermore, the 3 hours after, the intravenous injection of the 0.5% Evan SUBURU (Evans'blue) physiological-sodium-chloride-solution solution containing a DNP-As antigen was carried out at a rate of 2.5 mg/kg, and PCA reaction was caused.

[0037] The after [30 minutes] animal was slaughtered, according to Harada's and others approach (218 Journal of Pharmaceutics Pharmacology;23 and 1971), immersion neglect of the coloring matter leaked on the skin of the reaction section was carried out by carrying out the fragment of the reaction skin for 48 hours or more into the mixed solution of 0.3% sodium-sulfate water-solution:acetone = 3:7 (volume ratio), and exsorption coloring matter was extracted. Subsequently, the colorimetry of the extracted coloring matter was carried out by 620nm. As control, only an ointment base or olive oil was similarly applied instead of the above-mentioned sample offering agent, and the colorimetry of the coloring matter extracted by performing same actuation was carried out after that. From the quantum result of the coloring matter sampling volume (C) of the above-mentioned control application site, and the coloring matter sampling volume (D) of a sample offering agent application site, the rate of dye leakage control was computed by the following type. A result is shown in Tables 1-5.

Rate (%) of dye leakage control = $\{(C-D) / C\} \times 100$ [0038] [Example 3 of a trial] Trimming of the antinode flank skin of the five week ** Wistar system rat of the operation effectiveness to IV mold allergic response by the DTH reaction was carried out, subsequently 20microl spreading of a 2,4-dinitrochlorobenzene (DNCB, Wako Pure Chem make) acetone solution was done 20%, it was left for two weeks and sensitization was carried out. Trimming of the regions-of-back skin was carried out after sensitization formation, 20microl spreading of a DNCB acetone solution was done 0.5%, and cutaneous sensitization was induced. subsequently, the 0.1ml sample offering agent of the 0.1mg and liniments of the ointment obtained in the above-mentioned example and the example of a comparison -- each was applied to the rat skin DNCB reaction induction part by the same approach as the above-mentioned example 1 of a trial.

[0039] 24 hours after reaction induction, the erythema reinforcement of a reactive site was measured

with the color color difference meter (CR-200, Minolta Co., Ltd. make). As control, only an ointment base or olive oil was similarly applied instead of the above-mentioned sample offering agent, same actuation was performed after that, and erythema reinforcement was measured. From the measurement result of the erythema reinforcement (E) of the above-mentioned control application site, and the erythema reinforcement (F) of a sample offering agent application site, the rate of erythema control was computed by the following formula. A result is shown in Tables 1-5.

Rate (%) of erythema control = $\{(E-F) / E\} \times 100$ [0040] [Example 4 of a trial] The weight after the trial of the rat with which the example 3 of the effect above-mentioned trial over the whole body by weight change was presented was measured, and the effect of a side effect to the whole body was investigated. A result is shown in Tables 1-5.

[0041] In the examples 1, 2, and 3 of a trial, as for the external preparations for a skin disease therapy of this invention, the external preparations (examples 1 and 2 of a comparison) of adenocorticotrophic hormone content and the effectiveness more than an EQC were accepted. Moreover, with the external preparations of this invention, the side effect of a loss weight was not accepted to the side effect of a loss weight having been accepted with the external preparations of adenocorticotrophic hormone content in the example 4 of a trial. Moreover, in the external preparations (examples 4, 5, 7, 8, 10, 13, and 14 of a comparison) which contain a non steroid anti-inflammatory agent or DSCG independently, effectiveness was hardly accepted in the examples 1, 2, and 3 of a trial.

[0042]

[Effect of the Invention] The external preparations for a skin disease therapy of this invention are as above-mentioned, and though it has sufficient curative effect more than adenocorticotrophic hormone external preparations and an EQC, since there are few side effects, external preparations useful for the therapy of skin disease are obtained.

[Translation done.]